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Commentary Before the EPA SAB: Arsenic Panel

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Introduction

- The Panel's charge does not include assessment of developmental toxicity
- However,
  - Presentation is relevant to sensitive life stages
  - The Science Issue Paper invokes FQPA to recommend a 10X uncertainty factor to protect children

Developmental Toxicity Studies for Monomethylarsonic Acid (MMA^V) and Dimethylarsinic Acid (DMA^V)

- **GLP-compliant studies**
- **Daily oral administration during organogenesis**
- **Maternal and Fetal Toxicity at Highest Doses**
  - **Diaphragmatic Hernia in Rat Fetuses at 36 mg/kg/d DMA^V**
  - **Abortion with no Surviving Rabbit Fetuses at 48 mg/kg/d DMA^V**
- **Developmental No Observed Adverse Effect Levels (NOAELs)**

-MMA^V
- Rat: 100 mg/kg/d
- Rabbit: 7 mg/kg/d

-DMA^V
- Rat: 12 mg/kg/d
- Rabbit: 12 mg/kg/d

- **Maternal No Observed Adverse Effect Levels (NOAELs)**

-MMA^V
- Rat: 10 mg/kg/d
- Rabbit: 7 mg/kg/d

-DMA^V
- Rat: 12 mg/kg/d
- Rabbit: 12 mg/kg/d

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Margins of Exposure

- **Conservative (Based on total As intake)**
  - **MMA^V: 1,500 to 1,700**
  - **DMA^V: 2,700 to 3,000**
- **Unlikely Risk for Pregnant Women and Offspring**

Previously Published Developmental Toxicity Studies of MMA^V and DMA^V Are Not Adequate for Risk Assessment

- Three papers: Parenteral Exposures (Injection)
  - MMA^V, DMA^V and their Salts
  - Hamsters or Mice
  - Extremely High, Maternally Toxic Doses Only
    - 900 mg/kg ip
    - 100 mg/kg iv
  - Exencephaly: Both species
  - Insufficient Numbers of Animals

- Three papers: Oral Exposures
  - DMA^V
  - Rats or Mice
  - High, Maternally Toxic Doses
    - Mice: Maternal Toxicity ≥200 mg/kg/day; Cleft Palate ≥400 mg/kg/day
    - Rats: Maternal Toxicity ≥40 mg/kg/day; No consistent fetal effects up to 2400 mg/kg/day
  - Insufficient Dose-Response Information

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Summary of Currently Reported Studies

- Rats and Rabbits
- MMA^V and DMA^V
- Oral Exposures
- Doses Ranging from No-Effect to Maternally-Toxic
- Sufficient Numbers of Animals
- Methods and Results Presented Comprehensively
- No Evidence of Teratogenicity with MMA^V
- Diaphragmatic Hernias in Rats at High Dose of DMA^V
- No Observed Adverse Effect Levels (NOAELs) Established
- Margins of Exposures Estimated (1,500 – 3,000)
- Little or No Risk of Maternal or Developmental Effects in Humans

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Conclusion

- The FQPA 10X uncertainty factor for protection of children is not warranted based on developmental toxicity